REMARKS

Claims 1-12 are pending in this application, with claims 6-12 withdrawn from consideration. Claims 1, 2, 4 and 5 have been amended herein and new claims 13 and 14 have been added. Upon entry of this amendment, claims 1-14 will be pending, with claims 6-12 withdrawn from consideration.

The applicant respectfully submits that no new matter has been added. Support for the amendments to the claims is detailed below.

It is believed that this Amendment is fully responsive to the Office Action dated **December 14, 2006**.

Applicant's election with traverse of Group II, claims 1-5, as drawn to a polyclonal antibody specific for a phosphoylated linker region in Smad3 is acknowledged. Claims 6-12 have been withdrawn from further consideration by the Examiner as being drawn to non-elected inventions. (Office action paragraphs no. 2-7)

In paragraphs no. 3-5 of the present Office action, the Examiner responds to Applicant's arguments traversing the rejection. Applicant notes that in paragraph no. 3, the Examiner accepts the arguments, rejoining Groups I-III, and that in paragraph no. 4, the Examiner maintains the restriction between Group II and Groups IV to XIX.

However, the Examiner separately discusses the restriction between Group II and Groups VIII to XIII in paragraph no. 5, indicating that Groups VIII to XIII "**will be rejoined** as drawn to a method for assessing the activity of fibrosis stimulating signal in hepatic fibrosis and the efficacy of the molecular targeting therapy for hepatic-fibrosis, but will remain restricted to three Groups of methods using antibodies specific for the phosphorylated linker region in Smad2, Smad3, or Smad2 and Smad3 ..." (emphasis added).

However, Applicant notes that Groups VIII to XIII all include only claim 11, yet the Examiner has **withdrawn** claim 11 from consideration. Applicant respectfully submits that, based on the Examiner's statement, claim 11 should be rejoined and at least some portion of its scope considered. Applicant therefore respectfully requests consideration of claim 11.

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on October 9, 2003, No. 2003-351259. It is noted, however, that applicant has not filed a certified copy of the Japanese patent application No. 2003-351259 as required by 35 U.S.C. 119(b). (Office action paragraph no. 9)

The certified copy of the priority document is being filed concurrently in a separate paper.

The disclosure is objected to because of informalities. (Office action paragraph no. 10)

The Examiner states that the sentence bridging pages 3 and 4 is unclear.

The objection is overcome by the amendment to the specification. In the amendment to this paragraph, the phrase "with low homology" is deleted, and the term "linker region" is placed in quotation marks. This clarifies that the MH1 and MH2 domains are linked in the "linker region." The fact that the "linker region" has low homology among the Smad family is not necessary to this disclosure.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. (Office action paragraph no. 11).

Reconsideration of this objection is respectfully requested.

The Examiner has not explained why the title is considered not descriptive. The Examiner may desire a title limited to the claims that were not withdrawn due to the restriction requirement. However, the restriction requirement is under traverse, and it would be premature to amend the title in response to this requirement.

Claim 1 is objected to because of informalities. (Office action paragraph no. 12)

The Examiner states that there should be an indefinite article "a" at the beginning of the claim. The amendment to claim 1 includes an indefinite article at the beginning.

Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory matter. (Office action paragraph no. 13)

The Examiner states that claim 1 does not distinguish over naturally occurring polyclonal antibodies for the phosphorylated linker region in Smad2 and/or Smad3. The Examiner suggests inserting "isolated" or "purified."

The rejection is overcome by the amendment to claim 1, which inserts that the polyclonal antibody is "affinity-purified." The amendment is supported by the disclosure of affinity purification on page 13, lines 12-19. Due to the amendment to claim 1, claim 2 has been amended to be in independent form, retaining its original scope, and the dependence of claim 5 from claim 1 has been deleted. New claim 14 is supported by the deleted dependence of claim 5 from claim 3.

Claim 4 recites the limitation of "the mammal is a rabbit" for the polyclonal antibody according to any one of claims 1 to 3. There is insufficient antecedent basis for this limitation in the claim. (Office action paragraph no. 14)

The rejection is overcome by the amendment to claim 4 to delete the dependence from claim 1. Claim 4, as amended, depends only from claim 2, which does provide antecedent basis for "the mammal." New claim 13 is supported by the deleted dependence of claim 4 from claim 3.

Claim 5 recites the limitation of "the raised antiserum" for the polyclonal antibody according to any one of claims 1 to 3. There is insufficient antecedent basis for this limitation in the claim. (Office action paragraph no. 15)

The rejection is overcome by the amendment to claim 5. As amended, claim 5 depends only from claim 2, which does provide antecedent basis for the raised antiserum.

Claims 1, 2, 4 and 5 are rejected under 35 U.S.C. 102(a) as being anticipated by Furukawa et al. (Hepatology, September 27, 2003, 38:879-889). (Office action paragraph no. 16)

The rejection is overcome by Applicant's assertion that the subject matter in the Furukawa article is describing the work of the inventors.

Specifically, 12 of the 13 authors of the Furukawa et al. reference are the 12 inventors of the present application: F. Furukawa, K. Matsuzaki, S. Mori, Y. Tahashi, K. Yoshida, Y. Sugano, H. Yamagata, M. Matsushita, T. Seki, M. Nishizawa, J. Fujisawa, and Kyoichi Inoue. There is one author in the reference who is not an inventor of the present application: Yutaka Inagaki.

In support of Applicant's contention, Applicant has attached a Declaration under 37 CFR 1.132, signed by the eleven living inventors, stating that the twelve inventors of the present application were the inventors of the relevant disclosure of the Furukawa reference, and that Yutaka Inagaki did not make an inventive contribution.

Applicant therefore submits that the reference is disqualified as prior art by this Declaration under 37 CFR 1.132, in accordance with MPEP 715.01(c)(I) ("co-authorship").

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over [] Kretzschmar et al. (Genes & Development, 1999, 13:804-816) in view [of] Harlow and Lane (Antibodies, a Laboratory Manual, 1988, p. 93-94 and 142). (Office action paragraph no. 18)

The rejection of claims 1-5 over Kretzchmar is respectfully traversed, and reconsideration of the rejection is respectfully requested. Applicant here reviews the Examiner's arguments in the rejection.

Applicant first notes the Examiner's analysis of the scope of the claims on pages 8-9, in particular, the comments that claims 2, 4 and 5 are product-by-process claims. The Examiner is correct that these are product-by-process claims, but Applicant submits that it is **not** necessarily true that two antibodies made by different processes would be chemically indistinguishable from each other and would "function in the same manner."

The Examiner acknowledges that the Kretzchmar et al. reference does not teach polyclonal rabbit antibodies to the phosphorylated linker region in Smad2 and/or Smad3. The Harlow and Lane reference is cited for the general disclosure of use of mice, rats, hamsters and guinea pigs for production of antibodies, and for the use of polyclonal as opposed to monoclonal antibodies.

The Examiner states that:

> "the Board of Patent Appeals and Interferences has taken the position that once an antigen has been isolated, the manufacture of antibodies, which include polyclonal antibodies against it is *prima facie* obvious. See *Ex parte Erlich*, 3 USPQ 2d 1011 (PTO Bd. Pat. App.& Int. 1987), *Ex parte Sugimoto*, 14 USPQ 2d 1312 (PTO Bd. Pat. App. & Int. 1990).

That is, the issue in the rejection is, given that the phosphorylated linker regions of Smad2 and Smad3 are known, whether **any** antibodies directed against these regions would be obvious.

Ex parte Erlich is discussed in MPEP 2143.02, 2173.05(q), 2124. In MPEP 2143.02, the case is discussed with regard to predictability in the art, motivation, and expectation of success, and the MPEP emphasizes that the wording in the decision specifically uses the wording "in this case" and "this invention," that is, emphasizes that the decision is **very specific to the facts in that particular case**. In 2173.05(q), the issue discussed is the attempt to claim a process for use of monoclonal antibodies, without reciting positive steps; this is not relevant to the present rejection. MPEP 2124 deals with issues of whether references post-dating the invention can be used as teachings of the ordinary skill in the art, and again is not relevant to the present rejection.

In traversing the rejection, Applicant argues that the Examiner is improperly broadly interpreting the decision in *Ex parte Erlich*, and that the decision in that case does **not** generally state that "once an antigen has been isolated, the manufacture of antibodies ...against it is *prima facie* obvious," as the Examiner contends on page 10, lines 18-20. (Applicant cannot find such a statement in the text of the decision).

Applicant notes that the main issue in *Ex parte Erlich* appears to be an issue of unpredictability raised by Erlich, which the Board considered not to interfere with the "reasonable expectation of success." However, the contention of the Examiner appears to be that there is a

suggestion or motivation in the general art to prepare antibodies against **any** known protein. Applicant submits that that issue does not even appear to have been addressed in *Ex parte Erlich*.

The Examiner also cites *Ex parte Sugimoto*. The issue in that case has to do mainly with an Examiner's statement that: "It is well known to those skilled in the hybridoma art that production of the product (antibody) is greater when the hybridoma is grown in a mouse rather than in vitro." As with *Ex parte Erlich*, there appears to be no general statement in *Ex parte Sugimoto* that it is obvious to produce an antibody against any "antigen." Again, Applicant submits that the Examiner is improperly interpreting this decision.

Applicant notes that in general with regard to obviousness, MPEP 2143.01 states:

> "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art."

MPEP 2142 provides:

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure."

Applicant submits that there cannot be considered to be a teaching in the general art to prepare an antibody against **every** known protein. If there were, every conceivable antibody would be automatically *prima facie* obvious.

The issue here is whether there is some teaching, suggestion or motivation in Kretzschmar et al., in Harlow and Lane, or in the general art, to prepare an antibody against the phosphorylated Smad2 or Smad3 of Kretzschmar. Clearly there is no such suggestion in Harlow and Lane.

With regard to Kretzschmar, this reference notes that TGFβ exerts growth inhibitory and transcriptional responses through Smad2 and Smad3 (page 804, column 2), stating that these are TGFβ substrate receptors. The reference studied Ras-induced phosphorylation of Smad2 and Smad3 linker regions (p. 807, column 2), showing that these were phosphorylated under normal culture conditions, and increased by transfection with H-Ras. "The results suggest that the basal activity of the Ras pathway and, to a larger extent, the hyperactivation of this pathway by H-Ras or activated Mek1, cause the phosphorylation of Smad2 and Smad3."

The phosphorylation studies in the reference have been mainly carried out using ^{32}P-labeling and Western immunoblotting or immunoprecipitation. The anti-Smad2 and anti-Smad3 antibodies used appear to be generic antibodies **not directed against the phosphorylated linker region**.

Applicant also submits that these anti-Smad antibodies were completely adequate for detecting phosphorylated Smad2 and Smad3 in Kretzschmar's Western blotting and immunoprecitation studies, and therefore there appears to be no suggestion in Kretzschmar to prepare any other antibodies, in particular antibodies against the phosphorylated linker regions, in order to analyze these proteins.

Applicant also notes that in the summary of Kretzchmar on page 812, column 2, the reference discusses the nuclear accumulation of Smad2/Smad3. However, the reference is only an

investigation into this phenomenon, and this provides no suggestion or motivation for antibodies against the phosphorylated linker region of Smad2 or Smad3.

Claims 1-5 are therefore not obvious over Kretzschmar et al. and Harlow and Lane, taken separately or in combination.

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact the applicant's undersigned agent at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

In the event that this paper is not timely filed, the applicant respectfully petitions for an appropriate extension of time. Please charge any fees for such an extension of time and any other fees which may be due with respect to this paper, to Deposit Account No. 01-2340.

Respectfully submitted,

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Enclosure: Declaration Under 37 CFR §1.132

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